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	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	ErrorDefinitio	Errors
1	BRS	L1	3814	gene adj therapy	USPAT	2000/05/10 19:59			0
2	BRS	L2	2	small near fragment near homologous near replacement	USPAT	2000/05/10 19:59			0

(FILE 'HOME' ENTERED AT 20:08:15 ON 10 MAY 2000)

FILE 'MEDLINE' ENTERED AT 20:08:20 ON 10 MAY 2000

L1	0	S	HOMOLOGOUS DNA REPLACEMENT
L2	18	S	HOMOLOGOUS REPLACEMENT
L3	11505	S	GENE? THERAP?
L4	321	S	L3 AND REPLACEMENT
L5	10	S	L4 AND HOMOLOGOUS
L6	49572	S	(CF OR CYSTIC FIBROSIS)
L7	13	S	L6 AND L4
L8	13	S	L7 AND L3

L8 ANSWER 3 OF 13 MEDLINE
AN 1998015741 MEDLINE
DN 98015741
TI Review article: **gene therapy** in gastroenterology and hepatology.
AU Forbes S J; Hodgson H J
CS Liver Group Laboratory, Royal Postgraduate Medical School, London, UK.
SO ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (1997 Oct) 11 (5) 823-36. Ref: 98
Journal code: A5D. ISSN: 0269-2813.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199802
AB **Gene therapy** for diseases of the gastrointestinal tract is an exciting prospect because of the fundamental cure that is potentially available. The gastrointestinal system, and especially the liver, is an area that will be central to the development of **gene therapy**. Techniques for gene **replacement** include homologous recombination and gene augmentation. For the treatment of cancer antisense strategy, pro-drug activation systems and gene immunotherapy are being investigated. Gene-carrying vectors divide into viral- and non-viral-based vectors, each with advantages and limitations. The accurate delivery of these vectors to sufficient numbers of target cells in vivo is still a major barrier to clinical use. Diseases that may be helped by **gene therapy** include: gastrointestinal malignancies, viral hepatitis, the haemophilias, hypercholesterolaemia, alpha 1-antitrypsin deficiency, and metabolic diseases of the liver and **cystic fibrosis**. In this review we will outline the principles of **gene therapy**, delivery vectors under investigation, diseases that may benefit from this technology and some of the remaining problems to be overcome.
CT Check Tags: Human; Support, Non-U.S. Gov't
*Gastrointestinal Diseases: TH, therapy
Gastrointestinal Neoplasms: TH, therapy
***Gene Therapy**
Hemophilia A: TH, therapy
Hepatitis, Viral, Human: TH, therapy
*Liver Diseases: TH, therapy

8 ANSWER 4 OF 13 MEDLINE
AN 97420210 MEDLINE
DN 97420210
TI CFTR gene transduction in neonatal rabbits using an adeno-associated virus
(AAV) vector.
AU Rubenstein R C; McVeigh U; Flotte T R; Guggino W B; Zeitlin P L
CS Eudowood Division of Pediatric Respiratory Sciences, Johns Hopkins Medical
Institutions, Baltimore, MD, USA.
NC P01HL51811 (NHLBI)
SO GENE THERAPY, (1997 May) 4 (5) 384-92.
Journal code: CCE. ISSN: 0969-7128.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711
EW 19971104
AB Patients with **cystic fibrosis** develop lung disease after birth, therefore CFTR gene **replacement** therapy should be most efficacious in the neonatal period prior to the onset of pulmonary damage. An adeno-associated virus (AAV) vector, SA306 (Flotte TR et al Proc Natl Acad Sci USA 1993; 90: 10613-10617), which contains the AAV inverted terminal repeats flanking the human CFTR cDNA linked to an amino-terminal epitope tag, was used to transduce a human CFTR fusion protein into neonatal New Zealand white rabbits. Vector inocula of 1 x 10(5) to 5 x 10(10) particles were given by intratracheal instillation on day 3 of life and the rabbit lungs were studied at 3 or 4 days, 2-6 weeks, or 6 months after infection; the 2-6 week time-point corresponds to the completion of the alveolar phase of lagomorph lung development. Vector DNA was detected by an in situ polymerase chain reaction (PCR) using vector-specific primers at up to 6 weeks after inoculation. Human CFTR mRNA was detected by Northern analysis at up to 2 weeks after vector inoculation, and by a reverse transcriptase PCR assay at up to 3 weeks after infection. Epithelial expression of the human CFTR fusion protein was detected using antisera to both the human CFTR R domain and the amino-terminal epitope at up to 6 weeks after vector inoculation. Vector DNA, mRNA, or human CFTR immunoreactivity were not observed at the 6 month time-point. Rabbits infected with SA306 were clinically indistinguishable from their uninfected litter mates. These data indicate that CFTR gene transduction using an AAV vector is feasible in the neonatal rabbit, and that expression of vector-derived CFTR persists throughout the alveolar phase of lung development. The apparent lack of vector persistence after the alveolar phase may reflect dilution of transduced cells by further lung growth or a lack of transduction of pulmonary epithelial stem cells.
CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adenoviridae
Animals, Newborn
***Cystic Fibrosis Transmembrane Conductance Regulator: GE, genetics**
Gene Expression
***Gene Therapy: MT, methods**
Genetic Vectors
Immunohistochemistry
Lung: CH, chemistry
Polymerase Chain Reaction
Rabbits

*Transfection
RN **126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator)**
CN 0 (Genetic Vectors)

L8 ANSWER 5 OF 13 MEDLINE
AN 97358591 MEDLINE
DN 97358591
TI Incomplete rescue of **cystic fibrosis** transmembrane conductance regulator deficient mice by the human CFTR cDNA.
AU Rozmahel R; Gyomorey K; Plyte S; Nguyen V; Wilschanski M; Durie P; Bear C E; Tsui L C
CS Department of Genetics, The Hospital for Sick Children, Toronto, Ontario, Canada.
SO HUMAN MOLECULAR GENETICS, (1997 Jul) 6 (7) 1153-62.
Journal code: BRC. ISSN: 0964-6906.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
EW 19971005
AB We have used a mouse model to study the ability of human CFTR to correct the defect in mice deficient of the endogenous protein. In this model, expression of the endogenous Cftr gene was disrupted and replaced with a human CFTR cDNA by a gene targeted 'knock-in' event. Animals homozygous for the gene **replacement** failed to show neither improved intestinal pathology nor survival when compared to mice completely lacking CFTR. RNA analyses showed that the human CFTR sequence was transcribed from the targeted allele in the respiratory and intestinal epithelial cells. Furthermore, in vivo potential difference measurements showed that basal CFTR chloride channel activity was present in the apical membranes of both nasal and rectal epithelial cells in all homozygous knock-in animals examined. Ussing chamber studies showed, however, that the cAMP-mediated chloride channel function was impaired in the intestinal tract among the majority of homozygous knock-in animals. Hence, failure to correct the intestinal pathology associated with loss of endogenous CFTR was related to inefficient functional expression of the human protein in mice. These results emphasize the need to understand the tissue-specific expression and regulation of CFTR function when animal models are used in **gene therapy** studies.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Alleles
***Cystic Fibrosis: GE, genetics**
***Cystic Fibrosis Transmembrane Conductance Regulator: DF, deficiency**
***Cystic Fibrosis Transmembrane Conductance Regulator: GE, genetics**
Cystic Fibrosis Transmembrane Conductance Regulator: ME, metabolism
Electrophysiology
Forskolin: PD, pharmacology
Homozygote
Intestines: DE, drug effects
Intestines: PH, physiology
Mice
*Mice, Transgenic: GE, genetics
Phenotype
Recombinant Proteins: GE, genetics
Recombinant Proteins: ME, metabolism
Recombination, Genetic
Transgenes
RN **126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator)** ; 66428-89-5 (Forskolin)
CN 0 (Recombinant Proteins)

L8 ANSWER 10 OF 13 MEDLINE
AN 96066888 MEDLINE
DN 96066888
TI Recent advances in the application of **gene therapy** to human disease.
AU Hanania E G; Kavanagh J; Hortobagyi G; Giles R E; Champlin R; Deisseroth A B
CS Department of Hematology, University of Texas M.D. Anderson Cancer Center, Houston, USA.
NC P01 CA49639 (NCI)
P01 CA55164 (NCI)
SO AMERICAN JOURNAL OF MEDICINE, (1995 Nov) 99 (5) 537-52. Ref: 73
Journal code: 3JU. ISSN: 0002-9343.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199602
AB PURPOSE: To review the recent advances in the application of genetic modification strategies to the therapy of human diseases for which a molecular defect is known. METHODS: A computerized data bank search, the minutes of the National Institutes of Health (NIH) Recombinant DNA Advisory Committee published in the Federal Record, and reports of human clinical trials were used as data sources for this review. Clinical trials included in this review were published in the literature or approved by the NIH Recombinant DNA Advisory Committee. STUDY SELECTION: Evaluations of the efficacy of genetic modification strategies in clinical trials in human and in animal models are summarized. The design and outcome of the genetic modification strategies employed are reviewed for 16 marking trials, 16 gene **replacement** trials for molecular deficiency diseases, 3 chemoprotection and 4 chemotherapy sensitization trials, 11 cancer vaccine trials, 2 antisense oligonucleotide trials, and 3 molecular immunotherapy trials. DATA SYNTHESIS: The marking trials have shown that residual leukemia cells in the infused autologous marrow can contribute to relapse following autologous bone marrow transplants. The use of genetic modification for the **replacement** of missing or deficient genes in severe combined immunodeficiency, familial hypercholesterolemia, and **cystic fibrosis** has been associated with encouraging results so far. Clinical **genetic therapy** trials involving cancer vaccines, antisense oligonucleotides, adoptive immunotherapy with genetically modified T cells, delivery vectors containing interleukin-1 receptor inhibitor for arthritis, **replacement** strategies for storage diseases, and genetic suppression of human immunodeficiency viral replication are just commencing. CONCLUSIONS: The clinical application of genetic modification techniques has thus far been successful in the beginning phases of this field. These early results suggest that continuation of **gene therapy** trials designed to correct the molecular changes that lead to disease states in humans is warranted. Evaluation of such clinical trials in the future may be based on the analysis of assays for short-term surrogate endpoints, as well as on the therapeutic outcomes of the trial, such as survival or remission.

CT. Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Bone Marrow Transplantation
Clinical Trials
***Gene Therapy**
Gene Therapy: MT, methods
HIV Infections: TH, therapy
Immunotherapy
Neoplasms: TH, therapy

L8 ANSWER 12 OF 13 MEDLINE
AN 94167392 MEDLINE
DN 94167392
TI The new frontier: gene and oligonucleotide therapy.
AU Schreier H
CS Center for Lung Research, Vanderbilt University School of Medicine, Nashville, TN 37232-2650..
SO PHARMACEUTICA ACTA HELVETIAE, (1994 Jan) 68 (3) 145-59. Ref: 105
Journal code: P0E. ISSN: 0031-6865.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
EM 199406
AB Gene and oligonucleotide therapy are emerging as clinically viable therapeutic regimens for genetic, neoplastic, and infectious diseases. Approaches include insertion of human genes in viral vectors including recombinant retrovirus, adenovirus, adeno-associated virus, and herpes simplex virus-1, or recombinant bacterial plasmids. Viral vectors transfect cells directly; plasmid DNA is delivered with the help of cationic liposomes (lipofection), polylysine conjugates, gramicidin S, artificial viral envelopes or other such intracellular carriers. Major areas of interest include **replacement** of the **cystic fibrosis** transmembrane regulator gene and the alpha 1-antitrypsin gene; arrest of human immunodeficiency virus infection; and reversal of tumorigenicity and cancer immunization, among others. Oligonucleotide therapy is principally focusing on the same areas, although the approach is to halt DNA transcription or messenger RNA translation with code-blocking triple-helix-forming or "antisense" oligomers.
Contributions
from the pharmaceutical sciences are expected in pharmaceutical
chemistry,
drug delivery systems design, analytical chemistry, and biopharmaceutics.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
***Gene Therapy**
*Oligonucleotides
CN 0 (Oli

L8 ANSWER 13 OF 13 MEDLINE
AN 93282540 MEDLINE
DN 93282540
TI Molecular biology and therapy of disease.
AU Samara G; Sawicki M P; Hurwitz M; Passaro E Jr
CS Department of Surgery, UCLA School of Medicine, Wadsworth Veterans Administration Medical Center 90073..
SO AMERICAN JOURNAL OF SURGERY, (1993 Jun) 165 (6) 720-7. Ref: 7
Journal code: 3Z4. ISSN: 0002-9610.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199309
AB Molecular biology will have a profound impact upon the treatment of disease. Molecular techniques provide protein products for treatment of more diseases each year. The understanding of pathophysiology at the molecular level allows for improved drug design. Antisense technology can selectively control gene expression. **Gene therapy** is potentially the most important aspect of molecular biology. Physical and viral transduction mechanisms are being developed toward this end. Gene **replacement**, creation of antisense oligonucleotides, and prodrug strategies are being developed. Currently, gene **replacement** and prodrug therapy are feasible in at least a few cases, but further study will yield additional applications.
CT Check Tags: Human
Antisense Elements (Genetics)
Child
Cystic Fibrosis: CO, complications
***Gene Therapy**
Neoplasms: TH, therapy
Pancreatitis: ET, etiology
Pancreatitis: TH, therapy
Prodrugs: TU, therapeutic use
Respiratory Tract Infections: ET, etiology
Respiratory Tract Infections: TH, therapy
Transfection
CN 0 (Antisense Elements (Genetics)); 0 (Prodrugs)

FILE 'MEDLINE' ENTERED AT 19:52:47 ON 10 MAY 2000

L1	11505	S	GENE? THERAP?
L2	3	S	L1 AND (SMALL FRAGMENT HOMOLOGOUS REPLACEMENT)
L3	3	S	L1 AND (HOMOLOGOUS REPLACEMENT)
L4	18	S	HOMOLOGOUS RE

L2 ANSWER 1 OF 3 MEDLINE
AN 2000024476 MEDLINE
DN 20024476
TI Site-directed alteration of genomic DNA by **small-fragment homologous replacement.**
AU Goncz K K; Gruenert D C
CS Cardiovascular Research Institute, University of California, San Francisco, USA.
SO METHODS IN MOLECULAR BIOLOGY, (2000) 133 85-99.
Journal code: BU3. ISSN: 1064-3745.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200002
EW 20000204
CT Check Tags: Human
Blotting, Southern
Cell Line
Cystic Fibrosis Transmembrane Conductance Regulator: GE, genetics
DNA: AN, analysis
*Gene Targeting: MT, methods
Gene Therapy
Genome, Human
Liposomes: CH, chemistry
Mutagenesis, Site-Directed
Oligodeoxyribonucleotides
*Recombination, Genetic
Reverse Transcriptase Polymerase Chain Reaction
RNA: AN, analysis
Transfection
RN 126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator); 63231-63-0 (RNA); 9007-49-2 (DNA)
CN 0 (Oligodeoxyribonucleotides)

L2 ANSWER 2 OF 3 MEDLINE
AN 1999030259 MEDLINE
DN 99030259
TI Targeted replacement of normal and mutant CFTR sequences in human airway epithelial cells using DNA fragments.
AU Goncz K K; Kunzelmann K; Xu Z; Gruenert D C
CS Cardiovascular Research Institute, Gene Therapy Core Center and Cystic Fibrosis Research Center and Department of Laboratory Medicine and Stomatology, University of California, San Francisco, CA 94143, USA.
NC DK46002 (NIDDK)
DK47766 (NIDDK)
SO HUMAN MOLECULAR GENETICS, (1998 Nov) 7 (12) 1913-9.
Journal code: BRC. ISSN: 0964-6906.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199902
EW 19990204
AB Recent studies have reported that mutant genomic cystic fibrosis (CF) transmembrane conductance regulator (CFTR) sequences can be corrected in
transformed CF airway epithelial cell lines by targeted replacement with small fragments of DNA with wild-type sequence. To determine if the observed genotype modification following **small fragment**

homologous replacement (SFHR) was limited to transformed CF cell lines, further studies were carried out in both transformed and non-transformed primary normal airway epithelial cells. The endogenous genotype of these normal cell lines was modified following liposome or dendrimer transfection using DNA fragments with DeltaF508 CFTR sequence (488 nt, complementary single strands) designed to also contain a unique restriction enzyme cleavage site (Xho I). Replacement at the appropriate genomic locus by exogenous DeltaF508 CFTR DNA and its expression as mRNA was demonstrated by PCR amplification of genomic DNA and mRNA-derived cDNA as well as Xho I digestion of the PCR products. These studies show that SFHR occurs in both transformed and non-transformed primary human airway epithelial cells and indicate that single base substitution (the silent mutation giving rise to the Xho I site) and deletion or insertion of at least three consecutive bases can be achieved in both normal and CF epithelial cells. Furthermore, these studies reiterate the potential of SFHR as a strategy for a number of gene targeting applications, such as site-specific mutagenesis, development of transgenic animals, development of isogenic cell lines and for **gene therapy**.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Binding Sites: GE, genetics
Cell Line, Transformed
Cells, Cultured
Cystic Fibrosis: GE, genetics
Cystic Fibrosis: PA, pathology
*Cystic Fibrosis Transmembrane Conductance Regulator: GE, genetics
Deoxyribonucleases, Type II Site-Specific: ME, metabolism
DNA: AN, analysis
*DNA: GE, genetics
DNA: ME, metabolism
Epithelial Cells: CY, cytology
*Epithelial Cells: ME, metabolism
Eukaryotic Cells: CY, cytology
Eukaryotic Cells: ME, metabolism
*Gene Targeting
Mutation
Respiratory System: CY, cytology
Respiratory System: ME, metabolism
Reverse Transcriptase Polymerase Chain Reaction
RNA: AN, analysis

RN 126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator); 63231-63-0 (RNA); 9007-49-2 (DNA)

CN EC 3.1.21.- (endodeoxyribonuclease XhoI); EC 3.1.21.4 (Deoxyribonucleases, Type II Site-Specific)

L2 ANSWER 3 OF 3 MEDLINE

AN 97064949 MEDLINE

DN 97064949

TI Gene targeting of CFTR DNA in CF epithelial cells.

AU Kunzelmann K; Legendre J Y; Knoell D L; Escobar L C; Xu Z; Gruenert D C

CS Cardiovascular Research Institute, University of California, San Francisco, California 94143, USA.

SO GENE THERAPY, (1996 Oct) 3 (10) 859-67.
Journal code: CCE. ISSN: 0969-7128.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199707

EW 19970703

AB A goal of cystic fibrosis (CF) **gene therapy** is correction of the mutant CF transmembrane conductance regulator (CFTR) gene with wild-type (wt) DNA sequences to restore normal CFTR protein and function. Experiments with wtCFTR cDNA expression vectors have shown that the Cl ion transport phenotype associated with CF can be corrected to

resemble that in normal cells. An alternative to cDNA-based **gene therapy** strategies is one that corrects endogenous mutant sequences by targeted replacement with the wt homologue. To test whether such a strategy was feasible, a **small fragment homologous replacement** (SFHR) strategy was used to replace specific genomic sequences in human epithelial cells. Small fragments of genomic wtCFTR DNA were transfected into transformed CF epithelial cells. Replacement by exogenous CFTR DNA at the appropriate genomic locus and its expression as mRNA was indicated by: (1) allele-specific polymerase chain reaction (PCR) amplification of genomic DNA and mRNA-derived cDNA; and (2) hybridization of PCR products with allele-specific probes. In addition, the functional activity of CFTR protein was determined by whole cell patch clamp. Southern hybridization and patch clamp analyses suggested that approximately 1 in 100 CF cells underwent a homologous replacement event that resulted in intact Cl transport.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cell Line
*Cystic Fibrosis
Cystic Fibrosis: PA, pathology
*Cystic Fibrosis Transmembrane Conductance Regulator: GE, genetics
DNA: AN, analysis
Epithelium: CY, cytology
*Gene Targeting: MT, methods
Patch-Clamp Techniques
RNA: AN, analysis

RN 126880-72-6 (Cystic Fibrosis Transmembrane Conductance Regulator); 63231-63-0 (RNA); 9007-49-2 (DNA)

L4 ANSWER 14 OF 18 MEDLINE
AN 91043073 MEDLINE
DN 91043073
TI Gene replacement in parasitic protozoa [see comments].
CM Comment in: Nature 1990 Nov 8;348(6297):109
AU Cruz A; Beverley S M
CS Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115.
SO NATURE, (1990 Nov 8) 348 (6297) 171-3.
Journal code: NSC. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199102

L4 ANSWER 13 OF 18 MEDLINE
AN 92404749 MEDLINE
DN 92404749
TI Long regions of homologous DNA are incorporated into the tobacco plastid genome by transformation.
AU Staub J M; Maliga P
CS Waksman Institute, Rutgers, State University of New Jersey, Piscataway 08855-0759..
SO PLANT CELL, (1992 Jan) 4 (1) 39-45.
Journal code: BJU. ISSN: 1040-4651.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199212